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Clonidine and Prazosin Block the Iminodipropionitrile (IDPN)-Induced Spasmodic Dyskinetic Syndrome in Mice

JEAN LUD CADET,[1] TAMMY BRAUN AND WILLIAM J. FREED

Neuropsychiatry Branch, NIMH, WAW Building, St. Elizabeth's Hospital, Washington, DC 20032

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CADET, J. L., T. BRAUN AND W. J. FREED. *Clonidine and prazosin block the iminodipropionitrile (IDPN)-induced spasmodic dyskinetic syndrome in mice.* PHARMACOL BIOCHEM BEHAV **26**(4) 791–795, 1987.—The effects of drugs with selective action on alpha$_1$- or alpha$_2$-adrenoceptors were investigated on persistent head twitches, vertical neck dyskinesia, and the random circling behaviors induced by chronic intraperitoneal injections of IDPN. The alpha agonist clonidine and the alpha antagonist prazosin inhibited the IDPN-induced behavioral syndrome whereas the alpha antagonist yohimbine had no significant effect. These results suggest that dysregulation of a facilitatory noradrenergic input to cortical and/or subcortical motor areas may be involved in the abnormal movements caused by chronic treatment with IDPN.

Iminodipropionitrile Serotonin syndrome Adrenoceptors Prazosin Clonidine Yohimbine
Huntington's chorea Spasmodic torticollis

CHRONIC administration of iminodipropionitrile (IDPN) induces a characteristic syndrome which consists of lateral head-twitches, circling, hyperactivity, ataxia, and increased startle response [6, 8, 9, 14, 20, 33]. These behaviors last throughout the lifespan of the animals after cessation of IDPN injection but do not affect their longevity. These persistent changes are almost identical to the behavioral activation seen after acute injection of serotonin (5-HT) agonists ([2, 3, 16–18, 22, 23], Table 1). The 5-HT-induced syndrome has been used as a model to investigate neurotransmitter interactions in the causation of motor phenomena [2, 3, 16–18, 22, 23]. For example, it has been shown that it can be abolished by a series of drugs which act at different receptors. These include serotonergic [3,22], dopaminergic [18,23] and α_1-adrenergic antagonists [16] and gamma-aminobutyric acid agonists [17]. Receptors for these neurotransmitters are located in brain areas which are related to motor phenomena [34,40].

The IDPN-induced syndrome has been shown to be inhibited by various neuroleptics which may act at dopamine (DA), 5-HT, or norepinephrine (NE) receptors [9, 14, 33]. The relatively specific DA D-2 receptor antagonist, piquindone, also inhibits the IDPN-induced abnormalities [6]. The participation of other neurotransmitters in the phenomenology of these behavioral changes has not been fully investigated.

It has been proposed that the persistence of the IDPN-induced abnormalities makes it a good model for testing hypothesis about the biochemical interactions of transmitters which cause abnormal movements [14,33]. In effect, some of the behavioral and biochemical changes reported in the IDPN-treated animals mimic those reported in human basal ganglia disorders [6, 9, 14, 20, 33]. These may include Gilles de la Tourette's syndrome (GTS) [5], Huntington's disease (HD) [35,36], or spasmodic torticollis [11]. Since the etiology of these disorders is still unknown and since their neuropharmacological treatment is troublesome, the IDPN-induced syndrome may be useful in two ways. First, it can be used to investigate drugs that may be beneficial in the treatment of these neuropsychiatric disorders. Second, it may help to test biochemical hypotheses about the etiology of these neurodegenerative diseases.

Therefore, in order to continue to develop a more complete neuropharmacological profile for the IDPN-induced syndrome, the effects of some drugs that act at specific alpha-adrenergic receptors were tested for their ability to inhibit these persistent abnormalities. Alpha-adrenergic receptors have been described in the mammalian central nervous system [25,34].

METHOD

Male Swiss-Webster mice weighing between 20 to 30 g were used. The animals were kept on a 12-hr light-dark cycle with free access to food and water. At the beginning of the experiment, all animals received daily intraperitoneal (IP) injections of IDPN (100 mg/kg) or of an equal volume of saline until the abnormal behaviors developed (7 days). All animals which received the drug developed the dyskinetic movements. After an interval of at least one month, dyskinetic behaviors were tested using a dyskinesia scale ([9], Table 2). Horizontal locomotor activity was monitored using

[1]Requests for reprints should be addressed to Jean Lud Cadet, Department of Neurology, Columbia University, 630 west 168th Street, New York, NY 10032.

TABLE 1

COMPARISON OF BEHAVIORAL PHENOMENA RESULTING FROM SEROTONERGIC (5-HT) AGONISTS AND CHRONIC IDPN TREATMENT

	5-HT Agonists	IDPN
Hyperactivity	+	+
Ataxia	+	+
Lateral head weavings or shakes (laterocollis)	+	+
Backward head-tilting (retrocollis, vertical dyskinesia)	±	+
Random circling	+	+
Walking backwards	+	±
Forepaw treading	+	±
Stereotypy	+	+
Persistence	−	+

+=present; ±=may or may not be present; −=absent.

a photocell apparatus as previously described [13]. This apparatus does not measure stationary activities such as forepaw treading or other persistent stereotypic behaviors. The animals were randomly assigned to testing groups. Observations were made blind to the treatments used.

On the day of testing, each animal was put in an individual cage. They were left in the testing cage for 15 minutes before any testing was done. After a 15 min baseline recording, during which each animal was observed twice for 2 minutes, testing was stopped for about 5 min, while one of the three drugs (clonidine, prazosin, or yohimbine) or vehicle were being injected IP. The mice were then observed for another 30 minutes. The drugs were dissolved in saline in a volume of 10 ml/kg except for prazosin which was dissolved in distilled water with gentle heating. Prazosin was a gift from Pfizer Pharmaceutical Co. Yohimbine and clonidine were obtained from Sigma Chemical Co.

Unless otherwise indicated, at least eight animals received each dose of each drug. The data were analyzed using an analysis of variance followed by Scheffe multiple comparisons.

RESULTS

Prazosin

Following acute administration of the α_1-adrenergic antagonist prazosin, there was a significant reduction in the persistent abnormalities caused by chronic treatment with IDPN, $F(3,84)=18.46$, $p=0.0001$) (see Fig. 1A). Both 3 and 4 mg of prazosin produced significant inhibition of the behavioral syndrome at 15 and 30 min after the drug administration, while 2 mg did not produce a significant effect. Prazosin had comparable inhibitory effects on locomotor activity, $F(3,84)=11.06$, $p=0.0001$ (see Table 3).

Clonidine

The α_2-adrenergic agonist clonidine also significantly inhibited the IDPN-induced abnormalities, $F(3,105)=37.93$, $p<0.001$ (see Fig. 1B). The dosages were comparable in their effects and caused complete inhibition of the lateral head-weavings and the vertical spasmodic neck movements. Circling behaviors were also inhibited. Clonidine also produced a significant inhibition of locomotion, $F(3,105)=8.07$, $p=0.0001$ (see Table 3).

TABLE 2

DYSKINESIA SCORE

0	No abnormalities
1	Random circling
2	Vertical dyskinetic head and neck movements (retrocollis)
3	Circling and retrocollic movements
4	Lateral head weavings or shakings (laterocollis)

Modified from [9].

TABLE 3

EFFECTS OF SALINE, PRAZOSIN, CLONIDINE, AND YOHIMBINE ON ACTIVITY COUNTS IN IDPN-TREATED MICE

Treatment (mg/kg)	n	Baseline	0–15 min	15.1–30 min
Prazosin				
Saline	8	162 ± 79	188 ± 58	176 ± 46
2.0	8	136 ± 62	100 ± 60	30 ± 7‡
3.0	8	148 ± 67	66 ± 21*	18 ± 6‡
4.0	8	208 ± 87	92 ± 49	24 ± 10‡
Clonidine				
Saline	16	307 ± 55	341 ± 61	297 ± 58
0.050	8	245 ± 64	82 ± 53‡	13 ± 4§
0.100	8	355 ± 56	83 ± 38‡	8 ± 3§
0.200	8	197 ± 73	71 ± 40‡	15 ± 13§
Yohimbine				
Saline	8	222 ± 72	200 ± 68	198 ± 43
1.0	8	171 ± 86	166 ± 47	170 ± 59
2.0	8	223 ± 85	177 ± 73	208 ± 68
4.0	8	188 ± 62	232 ± 57	374 ± 46†

The values represent mean ± S.E.M. n=number of animals in each group.

*=$p<0.05$, †=$p<0.01$, ‡=$p<0.005$, §=$p<0.001$ in comparison to saline (Scheffe). The times listed represent times after injection of either saline or the three drugs.

Yohimbine

The α_2-adrenergic antagonist yohimbine (1–4 mg/kg) had no effect on the dyskinesia score (Fig. 1C). Yohimbine caused a significant increase in locomotion, $F(3,90)=4.09$, $p<0.009$. Post-hoc analyses revealed that the increase occurred during the second 15 min of observation only after the highest (4 mg/kg) dose of yohimbine (see Table 3).

DISCUSSION

Both the alpha$_1$-adrenergic antagonist prazosin [25] and the alpha$_2$-adrenergic agonist clonidine [32] suppressed the spasmodic dyskinesia induced by chronic treatment with IDPN. The drugs blocked all the tested aspects of the syndrome including random circling, laterocollis, and retrocollis but did not appear to inhibit other aspects of the IDPN-induced syndrome such as forepaw treading and intermittent backward walking that were not assessed in the present

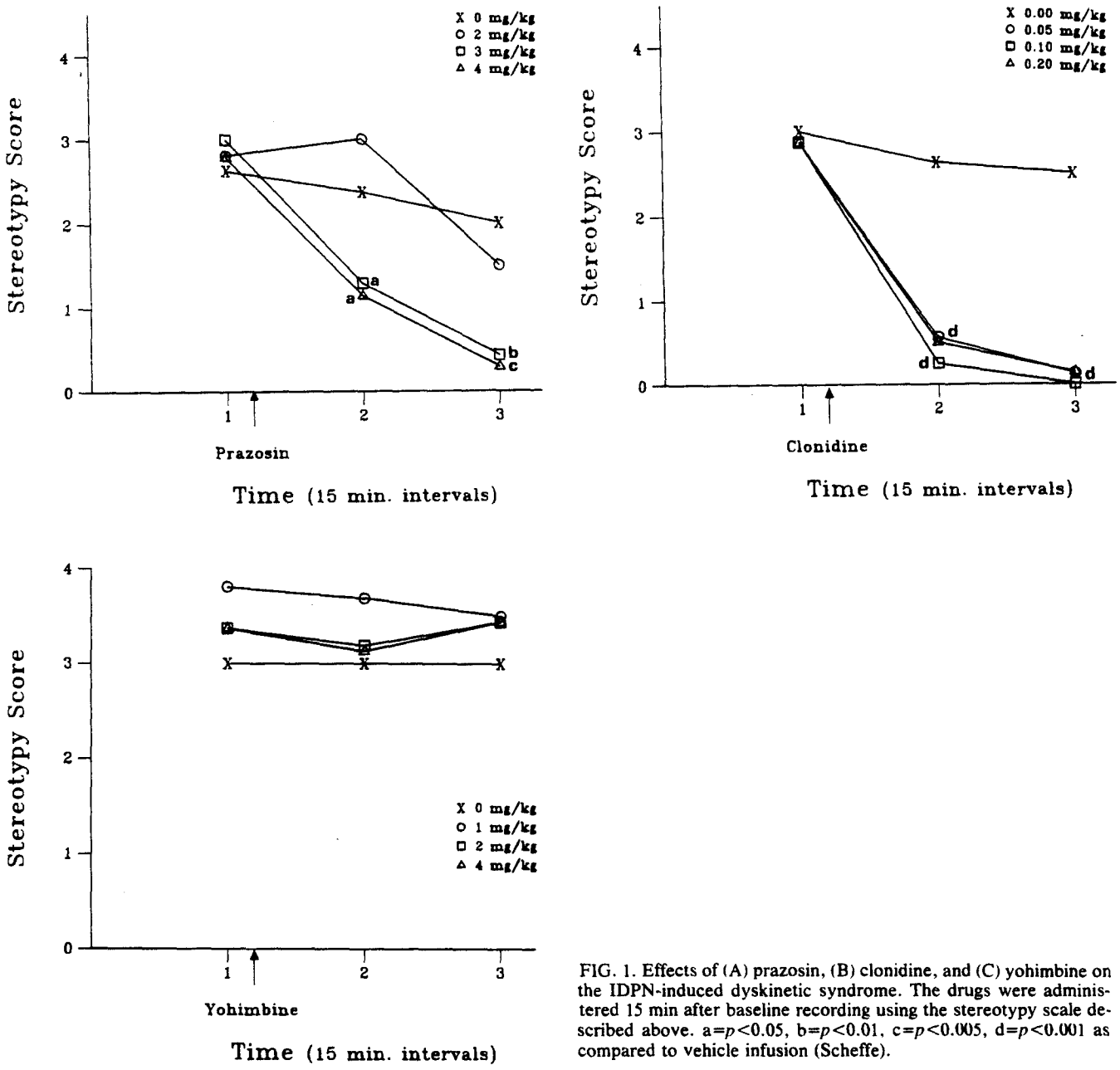

FIG. 1. Effects of (A) prazosin, (B) clonidine, and (C) yohimbine on the IDPN-induced dyskinetic syndrome. The drugs were administered 15 min after baseline recording using the stereotypy scale described above. a=$p<0.05$, b=$p<0.01$, c=$p<0.005$, d=$p<0.001$ as compared to vehicle infusion (Scheffe).

study. Despite the fact that locomotor activity was inhibited in concert with the IDPN-induced syndrome, the effects would not seem to be simply related to sedation, because even higher doses of these drugs do not cause significant sedation in normal mice [4,16]. The alpha$_2$-adrenergic antagonist yohimbine [15,30] had no inhibitory effect on the dyskinetic syndrome, but caused a significant increase in the locomotor activity.

Possible Role of the NE System in the IDPN-Induced Phenomena

The present results are similar to previous data which indicated that head-twitches induced by 5-HT agonists can be inhibited by prazosin and clonidine [2,16]. The inhibitory effects of prazosin probably involve blockade of postsynaptic alpha$_1$-adrenergic receptors found in brain areas that are related to movement [34] while the action of clonidine may be related to its inhibitory effects on cell firing in the locus coeruleus [19] or to its modulation of the serotonergic system [31]. It has been concluded that yohimbine may exacerbate the lateral head-twitchings caused by 5-HT agonists [16]. The discrepancies between that report and our findings are probably related to a ceiling effect introduced by the scale used in the present study. This interpretation is consistent with the demonstration of an increase in locomotor activity at the highest dose of yohimbine.

Our data suggest that the noradrenergic system may be directly involved or may exert a tonic facilitatory influence on cortical and/or subcortical systems involved in the manifestation of both the 5-HT-induced syndrome and the IDPN-induced spasmodic dyskinesia via activation of postsynaptic α_1-adrenoceptors. In fact, the NE system has

previously been implicated in the stimulatory effects of amphetamine [1, 24, 38] and of 5-HT agonists [16]. Furthermore, stimulation of the locus coeruleus also leads to behavioral activation that is inhibited by clonidine and prazosin but not by yohimbine [39].

Clinical Implications

Our results also suggest the possibility of using prazosin and clonidine in the treatment of human hyperkinetic disorders. Clonidine has been used with some degree of success in tardive dyskinesia [27] and in Gilles de la Tourette's syndrome [5,12]. The specific postsynatpic α_1-adrenergic antagonist prazosin has not, however, been tried clinically in the treatment in those disorders. Hyperkinetic phenomena are often attributed to a relative hyperfunction of the dopamine system in the basal ganglia [13]. Because of this thesis, neuroleptics have been the mainstay of the treatment of Huntington's disease (HD) which is characterized by choreoathetoid movements involving various muscle groups of the body [35]. Longterm treatment with neuroleptics is itself accompanied by the development of movement abnormalities such as tardive dyskinesia [27]. These persistent side-effects are a limiting factor in the use of these drugs in clinical neuropharmacology. Attempts to treat HD with other drugs such as GABA mimetics have not been very successful [35]. Since the IDPN-induced syndrome mimics several aspects of these human movement disorders, it has been suggested that it be used as a possible model for diseases of the basal ganglia [9, 14, 33]. Since neuroleptics have been successful at suppressing the abnormalities seen in both Huntington's chorea and in the IDPN-indiced syndrome, and since both syndromes can be exacerbated by 5-HT agonists [14,21], it is also plausible that the noradrenergic system may also play a role in the phenomena of human dyskinetic disorders. It has, indeed, been reported that the level of norepinephrine is relatively increased in the caudate of patients who suffer from Huntington's chorea [36], but the status of α_1-adrenergic receptors in the basal ganglia of patients with HD, tardive dyskinesia, or idiopathic dystonia remains to be evaluated.

In summary, our results raise the possibility of the existence of complex interactions between the dopaminergic, serotonergic, and noradrenergic systems in the causation of choreoathetoid and other dyskinetic phenomena. This hypothesis requires further testing. The IDPN-induced syndrome, because of its persistence, may be a good model to study interactions between transmitters involved in the causation of movement abnormalities.

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